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Role of Polyunsaturated Fatty Acid Derivative Flaxseeds in the Treatment of Dry Eyes- An Overview

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ABSTRACT

Introduction: Dry eye is the most common ocular disorder manifested by tear deficiency resulting in discomfort in eyes, visual disturbances, and instability in tear film with a surplus of alternative symptoms like burning of eyes, photophobia, tearing, ocular fatigue, and grittiness that hinder activities of daily living (ADL), therefore compromising the patient's quality of life.

Flaxseed is considered as an emerging food with nutritional characteristics loaded with essential polyunsaturated Omega-3 fatty acids with anti-inflammatory properties. The evidence shows a beneficial effect of nutraceutical supplements containing omega-3 and its derivatives (18: 3n-3; ALA) rich in flaxseeds and relieves symptoms of dry-eye. Therefore, the purpose of this study is to summarize the scientific-based evidence on the role of polyunsaturated fatty acid derivative flaxseed in the treatment of patients suffering from dry eye syndrome.

Methodology: The database collected from PubMed, PubMed Central (PMC), Cochrane library, Google scholar and research gate.

Discussion and Conclusion: At present, there are varieties of buffered formulations containing electrolytes, surfactants, preservatives available in the market that aggravate the patient's symptoms (tear film instability, poor epithelial healing) due to reported cytotoxicity. The nutraceutical, preservative-free supplements are, therefore, better alternatives for managing conjunctival dryness. The limited evidence and researches on flaxseed suggest standardized, well-designed Randomized Control Trials for delivering an accurate dose recommendation for dry eye patients.

Key Words: Dry eye syndrome, Omega-3 fatty acid, Flaxseeds (18: 3n3: ALA), Lacrimal gland, Tear film, Visual discomfort

INTRODUCTION

Dry eye is a global public-eye health issue characterized by corneal or conjunctival dryness accompanied by eye discomfort, visual disturbance, and tear film instability resulting in an altered pattern of daily living activities (ADL) with a significant effect on the quality of life.¹ Around 25% of patients with this syndrome consults eye care professionals.^{2,3} The prevalence of dry eyes reported in North-India is higher, ranging from 18.4% to 54.3% with the majority of the patient falling within the age groups of 21-40 years. The overall incidence ranges from 5% to 35% due to environmental pollution, climate conditions, life expectancy, lifestyles, and in-

creased opioid consumption.⁴ The international workshop on the dry eye (DEWS) classifies into three categories based on its causes, mechanism, and severity of the disease (2007).⁵ The tear film and ocular society (2017) reviewed it's the definition as a multiple factor disease characterized by loss of homeostasis of the tear film with ocular symptoms like increased tear film osmolarity, corneal surface desiccation that leads to instability in tear-film, ocular surface inflammation, and neurosensory anomalies.⁶

This condition is classified as episodic that occurs due to reduced blinking due to environmental or visual tasks saturating the tear stability or chronic disease aggravated by the

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similar environmental conditions but continue persistently with symptoms and ocular surface damage.⁷ Polyunsaturated fatty acid (PUFA) carries out a vital role during the treatment of dry eyes. An essential PUFA is found in omega-3 and omega-6 acting as precursors of eicosanoids, regulating the inflammatory process and immune responses.⁸ The Flaxseed is considered to be a nutritionally enriched food loaded with essential polyunsaturated Omega-3 fatty acids with anti-inflammatory properties.⁹ The other potential advantage of flaxseed includes the reduction of cardiovascular diseases, atherosclerosis, diabetes, cancer, arthritis, osteoporosis, autoimmune, and neurological disorders.¹⁰ The omega-6 group includes Linoleic acid (LA), gamma-linoleic acid (GLA), dihomogamma-linoleic acid (DGLA), and arachidonic acid (AA). Evidence suggests that the oral intake of omega-3 supplements help in controlling inflammation over the ocular surfaces and relieves the dry eye symptoms.¹¹ Therefore, the purpose of this study is to summarize the scientific-based evidence on the role of polyunsaturated fatty acid derivative flaxseed in the treatment of patients suffering from dry eye syndrome.

The information is collected from standard databases such as PubMed, PubMed Central (PMC), Cochrane library, Google scholar, and research gate. The search in PubMed, PubMed central was conducted using the Boolean operators: ("linseed oil"[Mesh Terms] OR ("linseed"[All Fields] AND "oil"[All Fields]) or "linseed oil"[All Fields] or ("flaxseed"[All Fields] and "oil"[All Fields]) or "flaxseed oil"[All Fields]) and ("keratoconjunctivitis sicca"[Mesh Terms] or ("keratoconjunctivitis"[All Fields] and "sicca"[All Fields]) or "keratoconjunctivitis sicca"[All Fields] or ("dry"[All Fields] and "eyes"[All Fields]) or "dry eyes"[All Fields] or "dry eye syndromes"[Mesh Terms] or ("dry"[All Fields] and "eye"[All Fields] and "syndromes"[All Fields]) or "dry eye syndromes"[All Fields] or ("dry"[All Fields] and "eyes"[All Fields])) and ("therapy"[Subheading] or "therapy"[All Fields] or "treatment"[All Fields] OR "therapeutics"[Mesh Terms] or "therapeutics"[All Fields]). In the Cochrane Library, a Medical Subject Headings search has performed with the following words flaxseed, dry eye syndrome with a limit of Cochrane reviews, trials, all date publication, and all years with word variations of flaxseed for dry eyes treatment/ syndrome.

Tear Film Mechanism

The healthy tear film signifies an exclusive fluid layer of approximately 3 μ m thick and 3 μ l in a volume covering the outer mucosal surface of the eye. This layer includes a mixture of

- a) Lipids-a thin layer (50 to 100nm) secreted from Meibomian glands located at the lid margin that aid in retarding evaporation of tears from the eye surface,

- b) Aqueous layer secreted from lacrimal gland which also secretes a variety of protein, electrolytes, and water thereby providing oxygen and nutrients to the corneal tissues and further removing the foreign bodies, and
- c) Mucin secreted by the specialized goblet cells in the conjunctival epithelium with some transmembrane mucin released into the tear film from the cornea and conjunctival epithelial cells that helps stabilize the tear film and forms the bulk of the tears.

The function of tear-film is to shield the ocular surface from the potentially pathogenic microorganisms. These are classified as 1) basal tears present on the ocular surface, 2) Reflex tears, activated by stimulation, and 3) closed eye tears activates during sleep. The tear turnover rate under standard condition is 1–3 μ l/minutes. Its activity is increased due to interaction with any stimulant/irritant particles. The signals received from both parasympathetic and sympathetic nerves via lacrimal, Meibomian, and goblet glands (parasympathetic innervations only) regulate the production of the tear film. These inputs from cornea and lid margins adjust the tear secretions by moving towards the lacrimal puncta and canaliculi from where they drain into the nasolacrimal system. The tear produced help in moistening the ocular surface by blinking mechanism. Full tears absorb through the nasolacrimal duct, and few portions are evaporated. The evaporation increases tear film osmolarity and lead to inflammation of the ocular surface and the lacrimal gland. These conditions lead to dry-eye that seeks an anti-inflammatory therapy to alleviate the symptoms. The high omega-3 fat content alpha-linoleic acid rich in flaxseed soften the secretion so that they can flow, thereby reducing the inflammation.^{12,13}

Aetiology/ Risk Factors of Dry Eye

Several factors are identified repeatedly within the epidemiological studies associated with dry Syndrome. Krenzer et al. reported that chronic androgen deficiency is related to Meibomian gland dysfunction.¹⁴ Evidence suggests that prolonged wearing of contact lens agitates the symptoms. In comparison, some studies determined that frequent drinking and smoking aggravates the symptoms of dry eyes.¹⁵ Employing antihistamine and antidepressants also exacerbate the symptoms. (Table 1) demonstrates some of the aetiological factors that increase its risk in the patients

Sources of Nutritional Supplement

The omega-3 (n-3) is derived from the family of polyunsaturated fatty acids (PUFA) that are essential but not produced by the body. These fatty acids belong to polyunsaturated fatty acid (n-3). They are the richest in EPA (eicosapentaenoic acid), DHA (docosahexaenoic acid), & ALA (alpha-linolenic acid).⁷ Flaxseed (*Linum usitatissimum*) is golden yellow or chromatic reddish-brown seed with structure incorporating short-chain PUFA of 18 carbons long alpha Li-

noleic acid (ALA) that is derived from various soluble and insoluble fibres, Phytoestrogens, along with the group of antioxidants.¹⁰ Flaxseed constitutes, additionally, the primary source of providing lignan precursors like secoisolariciresinol diglucoside (SDG) to prevent and alleviate lifestyle-related diseases. Its potential advantages are to cut back the symptoms of inflammation⁹ and the potential benefits of diminution of cardiovascular diseases, indurations of the arteries, neurological disorders.¹⁰ Some report reveals that one tablespoon (15 ml) of flaxseed oil in diet can meet and exceed the daily ALA needs.¹⁶ India ranks 4th with 0.15 million tons of total flaxseed production. Flaxseed is food consumed by humans while linseed as, used in the trade and for feed purposes.¹⁷ On the other hand, arachidonic acid (AA) is an omega-6 metabolite and the precursor of prostaglandins, leukotrienes, and different immune molecules. The omega-3 PUFA metabolites docosahexaenoic acid and eicosapentaenoic acid and fight with arachidonic acid to incorporate in cellular membrane phospholipids. The stability between these two PUFA ends up in an anti-inflammatory or a pro-inflammatory type in the organism.¹⁸ The study on animal models reported a higher level of (n-3) PUFA within the tissue layers of the retina and lacrimal system that helps in reducing the inflammation.¹⁹

Therapeutic Options for Dry Eye

At present, there are varieties of buffered formulations containing electrolytes, surfactants, preservatives, viscosity agents available in the market for managing instability in the precorneal tear-film and amplifying the tear film breakup time (TFBUT). The majority of it contains a similar composition (chemical properties+ preservatives used) (Table 2).

Evidence-Based Studies on Flaxseeds for Dry Eye Syndrome

Several studies reported cytotoxicity (benzalkonium chloride; BAK) and high prevalence of ocular surface disorders in preserved solutions/ lubricants leading to eye-burning, mild irritation to severe corneal and conjunctival scarring on installation.²⁰⁻²² Andrea Oleňík (2014) reports the beneficial effect of nutraceutical supplements formulations containing omega-3 sources relieves symptoms of dry eye syndrome.²³ Supplements rich in omega-3 fatty acids are less expensive to buy as compared to artificial tear formulations.²⁴

Hormonal Changes

Several studies emphasize the prevalence of hormonal effect of dry eyes in females, especially in the menopausal or post-menopausal age group.²⁵ This possibility might be due to the misbalance between the estrogen and androgen levels that influences the production and mechanism of layers of the tear film. The lower level of these hormones deactivates the activity of the Meibomian gland, alters the ocular surface

physiological conditions, and changes the receptor activity leading to dry eye.¹⁶ Flaxseed being richest in SDG, many studies on human and animal models reported that SDG and its metabolites mediate the lipoproteins and reduce the androgenic complications and oxidative preventions.²⁵ The topical application of novel androgenic hormone formulations to the eyelids demonstrates a beneficial effect with diminished side-effects in menopausal women's.²⁴ Cetisili (2015) conducted a study on 140 menopausal women and found that the estrogenic action of specific metabolites of flaxseed exhibits a protective effect by decreasing the symptoms and increasing quality of life among menopausal women. A study reports that consuming 90gms of flaxseed per day creates a positive effect on menopausal symptoms.¹⁹

Aging

The older adults are highly susceptible to two sorts of deficiencies because of the deficit lipid layer a) aqueous insufficiency that reduces aqueous secretion from the lacrimal gland and b) evaporation resulting in the unstable tear film.²⁰ The prevalence of aqueous insufficiency is 3.90% among men aged from 50 to 54 years as compared to 7.67% among men 80 years and older.²¹ Boerner (2000) experiment on 116 patients in an open-label clinical trial with omega-3 supplements and its derivatives Docosahexaenoic acid (DHA) and Alpha-linolenic acid (ALA) rich in flaxseed and found that 98% of a patient suffering from dry-eye syndrome reported an improvement in their symptoms.²²

Visual Display Unit

Working on a visual display unit, laptops, computers for more than 4 hours increases the risk of dry eye syndrome due to reduce blink mechanism that increases the rate of evaporation and causes eye fatigue and headaches affecting eye health and job performance. Buhargava et al. (2015) studied 456 individuals suffering from dry eyes and demonstrated that the group receiving a nutritional supplement of omega-3 fatty acid along with its derivative ALA diminished the symptom, thereby reduced the evaporation rate.²³

Animal Model

Li Z and colleagues (2014) studied a mouse model to investigate the efficacy of topical application of (n-3) Essential fatty acid (EFA) and hyaluronic acid formulations and found a significant effect of (n-3) EFA on clinical signs and inflammation as compared to hyaluronic formulation tears in dry eye disease. A similar study conducted on a mouse model and found that the topical application of omega-3 fatty acid and its derivative (18: 3n-3: ALA-flaxseed) reduces epithelial damage, the appearance of inflammatory cytokines and macrophage infiltration. The single route administration of flaxseeds either orally or topically was effective in treating

Combination Therapy

The nutritional supplement omega-3 fatty acid taken orally or topically might be an option for managing dry eye syndrome. A report suggested that these derivatives when combined with other anti-inflammatory agents, assist in reducing symptoms. A study conducted on a combination of Anti-inflammatory agents (Cyclosporin-A) with alpha Linoleic acid (ALA) and Linoleic acid (LA) formulations that seem to improve the TBUT and considered as a potential treatment for clinical symptoms and physiological changes associated with dry eye syndrome.²⁵ When other polyunsaturated fatty acids are combined, they exhibit the effect of omega-3 fatty acids and their derivatives (ALA: flaxseed). Thereby demonstrating substantial evidence of n-3 and its derivatives in the treatment of dry eyes.¹⁶ The low-dose oral doxycycline combined with flaxseed supplements when given in combination produces a beneficial effect in reducing inflammation.²³

Comparison between Flaxseed Oil, Oral and Topical Form

Pinheiro MN (2007) experimented on 38 feminine patients suffering from keratoconjunctivitis sicca. Sjögren's syndrome was arbitrarily allotted into 3 groups Gp-I receive flaxseed oil (1 g/day dose), Gp-II: flaxseed capsule 2 g/day dose, while Gp-III in placebo Gp for 180 days and found statistically significant changes ($p<0.05$) in the symptoms of ocular surface disease index, ocular surface inflammation, Schirmer-I test, and Tear film breakup time (TBUT) when compared to the placebo group. The results found that oral flaxseed oil and capsules 1 or 2 g/day reduced the ocular surface inflammation and symptoms of keratoconjunctivitis sicca and Sjögren's syndrome.¹⁸ Flaxseed capsules improve the symptoms as compared to artificial tear formulation. Omega-3 supplement containing flaxseed is cheaper than the tear formulations.

The similar study conducted which 36 patient receiving a daily dose of fish oil, containing Eicosapentaenoic acid (EPA) 450 mg and docosahexaenoic acid (DHA) 300 mg, and flaxseed 1000 mg oil for 90 days following baseline and final visits and found that these supplements increase the tear production and tear volume in a patient with the dry eyes syndrome. The application of an artificial tear (n-3) fatty acid-containing carboxymethylcellulose and glycerin, flaxseed and castor oil, and three osmoprotectants (levocarnitine, erythritol, and trehalose) when compared with an artificial tear (Refresh Optive Advanced [ROA]) over 242 subjects showed significant improvement ($P<0.05$).¹⁹ These findings suggest that the flaxseed play a beneficial role if administered either orally, topically or in oil form to treat the dry eye syndrome.

CONCLUSION

There are varieties of artificial tear buffered formulations of electrolyte, surfactant, preservatives in the market, that aggravate the symptoms of the patient due to reported cytotoxicity. Therefore, nutraceutical, preservative-free supplements are safer ways to treat conjunctival dryness. The omega-3 fatty acid and its derivatives: alpha-linolenic acid (ALA) rich in flaxseeds, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) with a chemical formula [18: 3(n-3); ALA, EPA, DHA] are essential acids helps to increase the tear substitute in the dry eyes. Flaxseed not only improves the quality of Meibomian gland secretion but also stimulates aqueous tear secretion via its anti-inflammatory properties on the dysfunctional lacrimal gland. Referring to many databases; we can suggest that flaxseed can play a beneficial role in treating dry-eye syndrome if applied either locally, topically, or in an oil-based form. The limited evidence and researches on flaxseed suggest a standardized, well-designed randomized controlled trials for delivering an accurate dose recommendation for dry eye patients.

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Table 1: Risk Factor and Symptoms of Dry Eye Syndrome.

Risk Factor	Etiological factors	Symptoms
Ageing	Age and feminine sex affected most. ²⁰	Lid laxity, sebaceous gland atrophy, metaplasia, decrease in tear volume with exaggerated tear break-up time and dry eye. ²¹
Hormonal changes	1) Menopausal and post-menopausal women 2) Women taking oral contraceptive pills	1) Significant decrease in tear production within the 6 th decade of life ²⁴ 2) Higher goblet cell density ²⁵
Environment	1) Relative humidity (RH) 2) Indoor environment. ¹⁴ 3) Exposure to sun, dust, pollution, and wind and extreme temperatures.	Low RH (30%) and high temperature influences the thermal climate and influence the precorneal tear film leading to corneal or conjunctival dryness. ¹⁵
Computer visuals	Computers, watching television, and prolonged reading. ¹²	Prolong working reduces the blink eye mechanism that causes the tears to evaporate and results in the dry eye ¹³
Vitamin-A deficiency	Corneal dryness (Xerosis) ¹⁹	Due to deficit diet in children and adults due to the consumption of alcohol, routine smoking habits.

Table 2: Evidence-based artificial tear formulation and combination therapies for Dry eye^{12,13}

Artificial Tear Formulation	
Optive Allergan	Optive Allergan provides the osmoprotection of the ocular surface against the high osmolarity of tear-film.
RestasisAllergan	It enhances the activity of tear production (cyclosporine)
Soothe	It helps in increasing the thickness of lipid layer post 1 min of instillation into the eye and produces effect after 1 month of application
Original Systane	It enhances the effect of cyclosporine A
Systane	Systane helps in maintaining the stability of the precorneal tear film, thus increases the tear break-up time (TBUT).
SystaneUltra	The pH of Systane ultra is 7.9 that helps strengthen the dynamic cross-linking of HP-Gaur and borate and permits the tear film to imitate like healthy eyes.
Combination therapies	
Restasis +original Systane were statistically better than Restasis + Refresh Tears (Allergan). ²¹	
Pieces of evidence suggested that Original Systanealone gives a positive result than Restasis + Refresh Tears (Allergan). ²¹	